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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/663,272	11/25/1996	LEONARD HARRISON	10308	8910

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	31

DATE MAILED: 07/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/663,272	Harrison et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 29, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *39, 40, 42, and 43* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☐ Claim(s) _____ is/are rejected.

7) ☒ Claim(s) *39, 40, 42, and 43* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. In view of Applicant's amendment and response, filed 4/29/02, the previous rejections of Claims 39 and 42 under the second paragraph of 35 U.S.C. 112 have been withdrawn. Additionally, the rejection of Claim 42 under the first paragraph of 35 U.S.C. 112 for the recitation of derivatives has been withdrawn.

2. Claims 39-40 and 42-43 are pending.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39-40 and 42-43 stand rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method of treating subjects with insulin dependent diabetes mellitus (IDDM) comprising administering to said subject the claimed peptides, for the reasons of record as set forth in Paper No. 28, mailed 10/25/01.

Applicant's arguments, filed 4/29/02, have been fully considered but they are not persuasive. Applicant argues that,

"Inasmuch as these proinsulin sequences are demonstrated to function as T-cell epitopes in humans at-risk of IDDM, the present invention discloses and enables the sequences, modifications and applications for diagnostic and/or therapeutic purposes in IDDM. In effect, any protein, peptide or auto-antigen demonstrated to be recognized by T-cells from individuals at-risk for an autoimmune disease, is not only a target but also a potential immunotherapeutic tool. The Examiner's attention is respectfully directed to the article by Harrison and Hafler entitled "Antigen-Specific Therapy for Autoimmune Disease" in Current Opinions in Immunology 12:704-711,2000, (attached as Exhibit A) which confirms that peptide autoantigens such as those identified by the present inventors are immunotherapeutic tools."

It remains the Examiner's position that Applicant has not established a link between the *in vitro* T cell proliferation assays of the specification and methods of treating and diagnosing IDDM. Thus, the specification fails to enable the

sequences of the instant claims as asserted by Applicant. While any protein, peptide or auto-antigen demonstrated to be recognized by T-cells from individuals at-risk for an autoimmune disease, *may* be a target and potential immunotherapeutic tool, potential is not the standard for patentability. Regarding the Harrison and Hafler reference, while the reference teaches several successful immunotherapies in animal models, the reference also points out that in human trials certain altered peptide ligands (APLs, which the peptides of the instant claims are) exacerbated disease in humans. What the reference fails to teach is that immunopeptide therapies have repeatedly failed in humans. See for example Gold et al. (1997), which teaches that with a T cell receptor peptide therapy that was successful in eliminating disease in an animal model, in human trials, "No meaningful changes were noted in physical examinations, vital sign measurements or in clinical laboratory values." Also see Marketletter (1999), which teaches that two diverse oral-tolerance-based immunopeptide drugs, Myloral and Colloral, both successful in animal models, were complete failures in human trials. Thus, it remains the Examiner's position that immunopeptide therapy must be considered highly unpredictable and must be considered on a case-by-case (or peptide-by-peptide) basis. Therefore, the data of Example 11 of WO 01/30378, in which insulin was supplied as an immunotherapeutic agent in humans, cannot support the multitude of GAD/proinsulin peptides of the instant claims.

Applicant argues that "T-cell proliferative responses are well-known to vary greatly between individuals depending on factors such as the precursor frequency of antigen-specific T-cells, the number of assay replicates, HLA allele types and the stage of disease. The statistical treatment summarizing the results achieved in accordance with the present invention, clearly demonstrates that despite large variances, differences between IDDM at-risk and control subjects were significant. This conclusion is irrefutable." While Applicant may assert the irrefutability of the instant data, it appears that the p value disclosed for the GAD peptide in Example 4 would not be considered significant as said value is disclosed to be <0.018 whereas a p value of <0.01 is generally considered to be significant. Regardless, the specification fails to establish a link between T cell proliferation assay results and therapeutic or diagnostic efficacy.

Applicant further asserts that "the art is replete with considerable and reliable proof that peptide antigen-specific preventive therapy in animal models of experimental and spontaneous autoimmune disease is predictable." It is the Examiner's position that the art is just as replete with reliable proof that peptide antigen-specific preventive therapy is unpredictable in humans, see for example Gold et al. and Marketletter. Further, APL treatment has been shown to be not only unpredictable in humans, but dangerous as well. See for example Anderton et al. (2001), which teaches "This unpredictability led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders.[15] Such an approach in an outbred human population might aggravate rather than reduce pathology."

5. The following is a new ground of rejection necessitated by Applicant's amendment.

6. Claims 39 and 42 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, X_2 is any amino acid sequence from 10 to 13 residues, is not supported by the specification.

At page 3, lines 7-10 the specification discloses X_2 of 10 to 50, 10 to 30, or 10 to 15 amino acids, but not X_2 of 10 to 13 amino acid residues.

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire

on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center at (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
Technology Center 1600
July 12, 2002

Patrick J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600